## REMARKS

### A. STATUS OF THE CLAIMS

Claims 1-31 were originally filed in this application. In response to a Restriction Requirement dated May 31, 2001, Applicants elected Group V, corresponding to claims 1-13 and 23-31. Claims 2 and 14-22 were canceled in the Response filed on January 23, 2002. Claims 32 and 33 were added in the Amendment and Response, mailed October 1, 2002, to the Office Action dated May 1, 2002. Claim 8 has been canceled herein without prejudice or disclaimer and Applicants maintain the right to pursue the subject matter of these claims in a continuing application. Claims 1, 9-13, 23 and 30-33 have been amended herein. Support for these amendments can be found at least on page 7, lines 5-6 of the specification. No new matter has been added. Thus, claims 1, 3-7, 9-13 and 23-33 are currently pending and are provided in Appendix B.

### B. CLAIMS 1, 3-7, 9-13 AND 23-33 FULFILL THE REQUIREMENTS OF 35 U.S.C. §112, FIRST PARAGRAPH.

The final Office Action mailed on December 10, 2002 rejects claims 1, 3-13 and 23-33 under 35 U.S.C. §112, first paragraph based on the specification lacking a disclosure that enables any person skilled in the art to use the invention commensurate with the scope of the claims. The Action states that the term "phosphorothioate" was given its broadest reasonable interpretation in light of the specification. In light of this interpretation the claims are said to encompass any phosphorothioate compound and its active metabolites, which renders the claim scope very broad. The Action further states that the specification is not enabling for inhibition or prevention of metastases of any tumor by using phosphorothioate and active metabolites thereof.

In addition, the Action states that the specification is not enabled for the inhibition or prevention of tumor metastases *in vivo* by using phosphorothioate and active metabolites thereof.

The standard for determining whether the specification meets the enablement requirement is that the claimed invention be enabled so that any person skilled in the art can make and use the invention without ***undue experimentation***. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), as cited in the MPEP at 2164.01.

The initial burden is on the Examiner to establish a reasonable basis to question enablement, as provided in MPEP section 2164.04:

> "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." citing *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)

The Action lacks sufficient ***evidence*** to support a determination that the disclosure does not satisfy the enablement requirement and does not provide a reasonable basis to question the enabled scope of the present claims. Further, the action relies on faulty reasoning, born out of a misunderstanding of the Milas and Kanclerz references, to support the reasoning provided in the Action for doubting the objective truth of the statements provided in the specification.

Applicants traverse the rejection. In the interest of progressing prosecution of the application Applicants have amended claims 1, 11-13, 23, and 30-33 to read "aminoalkylphosphorothioate" instead of "phosphorothioate" and have canceled claim 8 without prejudice or disclaimer. Support for the amendments can be found at least on page 5, lines 16-19; page 7, lines 5-6; page 11, lines 13-14; and page 13, lines 1-19. Further support for the amendments can be found in issued U.S. Patents number 5,488,042; 5,567,686; 5,869,338; and 5,891,856, which are incorporated by reference in the instant specification on page 5, lines 16-19

and made of record in the information disclosure statement filed on September 6, 2000. One of ordinary skill in the art would readily recognize that aminoalkylphosphorothioate or active metabolite thereof would include the exemplary compound WR-2721 and other related compounds as described in the specification on page 13, lines 1-19. The specification enables one of ordinary skill in the art to practice the invention commensurate in scope with the invention as claimed without any undue experimentation.

The Action relies on four arguments as a basis for questioning the enablement of the present claims (1) the term "phosphorothioate" renders the claim scope as broad, (2) the specification fails to specifically define at what concentration of phosphorothioate is "subcytoprotective," and (3) the Kanclerz reference is cited to support the premise that the specification fails to specifically define at what concentration of phosphorothioate is "subcytoprotective."

First, Applicants note that evidence supporting the contention that the scope of the claims directed to administration of a phosphorothioate as not being enabled has not been presented. The reasoning provided in the final Office Action is that different chemical compounds could have positive or negative effects in inhibiting metastasis and the degree of tumor radioprotection afforded by WR-2721 varies with the type of tumor and assay endpoint. This reasoning is based on the assumption that radioprotection is equated to the invention as claimed. This assumption is an error. For example, the Milas reference is directed to the use of WR-2721 to reduce ***enhanced*** metastasis associated with radio- and chemotherapy. Milas does not teach any effects on metastasis in the absence of radio- or chemotherapy. In fact there is no teaching of inhibiting metastasis or reducing the number of metastases at a dose of 400 mg/kg. Milas shows that treatment with WR-2721 is shown to reduce the radiation or chemotherapy ***induced*** metastases

and lowers the number of metastases to control levels, which are the number of metastases observed without radiation. Thus, Milas demonstrates radioprotective effects of WR-2721 in combination with radiation or chemotherapy, and not inhibition of metastasis or reduction in number of metastases in the absence of radio- or chemotherapy. The studies are not comparable and should not be equated. Therefore, the variability in tumor response to the radioprotective effects of WR-2721 cannot be used as evidence for unpredictability of the invention as claimed. In the absence of variable effects of WR-2721, no evidence or reasoning is provided for the lack of enablement for the scope of the invention as claimed.

Second, Applicants contend that the dose of aminoalkylphosphorothioate, as presently claimed, is explicitly stated in the claim, for example claim 1 states in part "...administering to said animal a subcytoprotective dose of ***10 mg/kg to 150 mg/kg***..." (emphasis added). Thus, the Action's reliance upon the lack of definition of what concentration of phosphorothioate is subcytoprotective does not rebut or provide sufficient evidence to doubt the enablement of the invention as claimed.

Third, the Kanclerz reference is cited in support of the specification failing to specifically define at what concentration of phosphorothioate is subcytoprotective. Applicants note, as above, that the dose of phosphorothioate administered is explicitly stated in the claim. The relevance of what dose of phosphorothioate is subcytoprotective in light of the claimed dosages, *e.g.*, of 10 mg/kg to 150 mg/kg, as well the relevance of the argument to the enablement of the pending claims is unclear to the Applicants. Furthermore, as argued in the previous responses, data is provided in the specification with respect to different tumor cells. Examples of various tumors including the sarcoma SA-NH, the adenocarcinomas Mca-K and Oca-I are provided in the specification, see the specification at least at page 25.

In addressing the rejection based on the lack of enablement for *in vivo* use, the Action relies on the mere statement that the specification fails to provide adequate guidance and evidence for use of the claimed invention *in vivo*. The burden is on the Examiner to provide reasoning and evidence of non-enablement. The mere statement of such does not meet the standards set forth for demonstrating a lack of enablement. Even so, Applicants point to the specification at pages 24-25 where the effectiveness of an exemplary aminoalkylphosphorothioate, as presently claimed, on multiple tumor systems is shown.

The effectiveness of the current invention against various tumors has been established in this response and the prior response dated October 1, 2002. For example, Tables 1 and 2 on page 25 demonstrate the effectiveness of a single dose of 50 mg/kg of WR-2721 for various tumor types (SA-NH, Mca-K, and Oca-I). Similarly, dosage schedules of 50-100 mg/kg every other day for 6 days (page 28, line 9) and a dose 50 mg/kg every third day (pg. 23, line 18) are demonstrated. Therefore, both single dosage and multiple dose schedules are exemplified in the specification. Furthermore, pages 23-24 of the specification describe the assaying of tumors in mice and the results of those experiments are disclosed and illustrated in FIGs. 1 and 2. The *in vivo* data provided in the specification has not been rebutted by any evidence or reasoning provided in the final Office Action or in previous Actions. The demonstration of treatment in mice is adequate enablement of the claimed invention; proof of efficacy in clinical trials involving humans is not a requirement for patentability. *See In re Brana,* 51 F.3d 1560 (Fed. Cir. 1995). *See also Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994) ("Title 35 does not demand that such human testing occur within the confines of Patent and Trademark (PTO) proceedings."). The claims are enabled for *in vivo* use. The Applicants

have taught such use in their specification. Absent any evidence to the contrary, the invention as claimed is enabled by the instant specification.

Applicants note that the final Office Action dated December 10, 2002 and the previous Office Action dated August 23, 2001 asserted that c-myc phosphorothioate oligonucleotides are phosphorothioates and these phosphorothioates protect against metastasis. Applicants disagree with the interpretation of phosphorothioate due to the fact that a c-myc phosphorothioate oligonucleotide is a polymer of nucleotides with a phosphorothioate backbone. Any activity of this composition is due to the nucleic acid sequence not the oligonucleotide backbone. In the least this compound would be classified as a phosphorothioate oligonucleotide not a phosphorothioate. However, this rejection is moot in light of the amendments herein.

In light of the facts presented above the Action has failed to provide a factual basis for questioning the enablement of the invention as claimed. In the interest of judicious prosecution, Applicants request the reconsideration and withdrawal of the rejection.

**C. THE REJECTIONS UNDER 35 U.S.C. §103(A) ARE OVERCOME.**

The final Office Action mailed December 10, 2002 rejects 1) claims 1, 3-13 and 30-32 over Milas *et al.*, 1984 (IDS reference C51) in view of Kanclerz *et al.*, 1988; 2) claims 1, 23 and 25-29 over Milas *et al.*, 1984 (IDS reference C51) in view of Kanclerz *et al.*, 1988 and further in view of U.S. Patent 5,837,696 and Antras-Ferry *et al.*, 1997 (IDS reference C2); and 3) claims 1, 23 and 24 over Milas *et al.*, 1984 (IDS reference C51) in view of Kanclerz *et al.*, 1988 and further in view of Gately *et al.*, 1997 (IDS reference C13) as being unpatentable under 35 U.S.C. §103(a).

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness. In order to establish a *prima facie* case of obviousness, under 35 U.S.C. § 103, three basic criteria must be met: (1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2142. *See also In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art, and not based on applicant's disclosure).

In response to the above rejections Applicants submit that a proper *prima facie* case has not been made. Applicants' response to each rejection is provided below.

**1. Claims 1, 3-7, 9-13 and 30-32 are not obvious in light of Milas *et al.*, 1984 in view of Kanclerz *et al.*, 1988.**

The Action rejects claims 1, 3-13 and 30-32 under 35 U.S.C. §103(a) as being unpatentable over Milas *et al.*, 1984, IDS reference C51 ("Milas"), in view of Kanclerz *et al.*, 1988 ("Kanclerz"). The Action maintains the rejection based on the premise that Milas teaches that WR-2721 greatly reduces the spontaneous metastases ***induced*** by cyclophosphamide (CY) and whole body irradiation (WBI) in mice with fibrosarcoma injected i.v. into the mice. The Action cites Milas in view of Kanclerz that purportedly teaches the use of three different doses 0.05 g/kg, 0.1 g/kg, and 0.2 g/kg for 10 consecutive days to suppress extrapulmonary metastases. As described in detail below the references cited ***do not*** contain a suggestion or motivation to

modify the reference or to combine reference teachings; ***do not*** provide a reasonable expectation of success; and above all ***do not*** teach or suggest ***all the claim limitations***.

Applicants submit that a fundamental misunderstanding of the Milas and Kanclerz references has been made and the relevance of the references to the claimed invention has been misplaced. Claim 1 as amended reads as follows:

> "A method for reducing the number of metastases in an animal exhibiting a primary tumor comprising administering to said animal a dose of 10 mg/kg to 150 mg/kg of an aminoalkylphosphorothioate or active metabolite thereof, wherein the number of metastases is reduced."

Claim 1 ***does not*** recite or require any ***induction or enhancement*** of metastasis as is taught in Milas, and ***does not*** recite or require treating established metastases, as taught in Kanclerz.

A caveat to the Milas reference is that both artificial and spontaneous metastasis are still observed, thus metastasis itself has not been reduced only ***metastasis enhancement*** generated by the insult of either radiation or chemotherapy. No such treatment is recited or required in Applicants claims. In order for Milas to observe a reduction in the enhancement of metastasis the animal must be treated with radioactivity or a chemotherapeutic. The requirement for treatment is evinced by the last sentence of Milas that reads: "This effect of WR-2721 could be therapeutically beneficial when the drug is combined with tumor radio- or chemotherapy." Thus, Milas does not describe, alone or in combination with Kanclerz "A method for ***reducing the number of metastases*** in an animal ***exhibiting a primary tumor*** comprising administering to said animal a dose of 10 mg/kg to 150 mg/kg of an aminoalkylphosphorothioate or active metabolite thereof, wherein the number of metastases is reduced." A distinction must be made between a treatment that damages normal tissues and induces an enhancement of metastasis (*i.e.*, inherent levels of metastasis are not shown to be effected), both artificial and spontaneous, and a

treatment that alone inhibits metastasis or reduces the number of metastases. The invention as claimed is not related to the administration of any type of treatment in conjunction with aminoalkylphosphorothioates nor does it require insult to the tissue to induce an enhancement of metastases.

**a. The References Do Not Contain A Suggestion Or Motivation To Combine**

In view of the statements above, a valid *prima facie* case of obviousness has not been made because "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." MPEP 706.02(j). *See also In re Fine*, 837 F.2d at 1074; *In re Jones*, 958 F.2d at 351. The Action contends that a person of ordinary skill in the art would combine the dosages in Kanclerz, which allegedly teaches the use of 0.05 g/kg, 0.1 g/kg and 0.2 g/kg of WR-2721, for inhibiting metastasis or reducing the number of metastases, with Milas *et al.*, which teaches that WR-2721 when given intraperitoneal (i.p.) is a radioprotector at a dose of 400 mg/kg.

However, Milas teaches the use of WR-2721 as a **radioprotector** used in combination with radiotherapy or chemotherapy to protect normal cells from being harmed by cancer treatments and Kanclerz teaches, marginally, growth inhibitory effects of WR-2721 on established micrometastases. The results of Kanclerz are *ambiguous* in that the dosage range cited, 0.05g/kg, 0.1g/kg and 0.2g/kg, could result in an enhancement of metastases growth, which is contrary to the claimed invention. In other words, the cited reference actually *teaches away* from the claimed invention in that lower doses of aminoalkylphosphorothioate are not effective, see Kanclerz Fig 4. These references alone or in combination do not teach inhibition

of metastasis or reduction in number of metastases at the doses required in the present claims. In fact, Milas and Kanclerz teach a different method with respect to the claimed invention, and as such, there is no suggestion or motivation to combine these references to achieve the claimed invention. Furthermore, the claimed invention would produce unacceptable results in view of Kanclerz. Thus, a rejection based on Kanclerz is "the very antithesis of obviousness." *In re Buehler,* 185 U.S.P.Q. 781, 787 (C.C.P.A. 1975).

Accordingly, there is no motivation or suggestion in Kanclerz that would lead one of ordinary skill in the art to combine the dosage range, 0.05g/kg, 0.1g/kg and 0.2g/kg, with the Milas reference, or vice versa. In fact, in the event that these references were combinable they still would not provide all the limitations of the claimed invention because neither reference describes methods of inhibiting metastasis or reducing the number of metastases.

**b. The References Do Not Provide A Reasonable Expectation Of Success**

To establish a valid *prima facie* case of obviousness under, 35 U.S.C. § 103(a), there must also be a reasonable expectation of success and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (MPEP 706.02(j)).

Referencing the argument provided above, Kanclerz teaches treating established metastases with WR-2721 and Milas teaches WR-2721 as a radioprotector, a person of skill in the art would not have a reasonable expectation of successfully inhibiting metastasis or reducing metastases according to the claimed invention. One would not know to use the claimed dose of aminoalkylphosphorothioates or active metabolites to achieve inhibition of metastasis or reduce the number of metastases, or know to treat an animal exhibiting a primary tumor. A person of ordinary skill in the art would not have any expectation of achieving the inhibition of metastasis or reducing the number of metastases.

### c. The References Are Not Enabling And Do Not Teach Or Suggest All Claim Limitations

For a reference to render obvious a claimed invention, it must be enabling. MPEP § 2121.01. According to the MPEP, a "reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of invention." *Id.*; *see also Ex Parte Gould*, 231 U.S.P.Q. 943 (B.P.A.I.). The Court of Appeals for the Federal Circuit has stated, "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *Id.* (citing *In re Donohue*, 766 F.2d 531, 226 U.S.P.Q. 619 (Fed. Cir. 1985).

The Kanclerz reference reports studies on the effects of radiosensitizers and radioprotectors on ***established*** micrometastases and ***not*** studies regarding inhibition of metastasis or reduction of the number of metastases as claimed in the present invention. Support for this position is provided by the statements of Kanclerz on page 310, left column, second paragraph under "Mice and tumors" that read:

> "Metastatic disease was induced by s.c. transplantation of tumor tissue fragments of approximately the same volume into the mouse tails as described previously. [reference omitted] The primary tumors metastasized from the tails and were removed by amputation at approximately 2 weeks after implantation when their volumes were 40+/-10 $mm^3$. 24 hours thereafter, animals were randomized into two groups: one group received treatments with radiosensitizer or WR-2721 and the other group received equal volumes of saline."

that is, tumor cells that have already metastasized prior to treatment. The statement that "suppression of extrapulmonary metastases was observed," in no way provides evidence of inhibition of metastasis due to the fact that metastasis has occurred prior to treatment. One can not inhibit something that has already occurred. The experimental evidence supports growth inhibition of the established metastases not a reduction in the number of metastases. The data

supporting this contention is tenuous at best due to the lack of proper controls, *i.e.*, a non-tumor bearing drug treated animal. Extrapulmonary tissue was simply *weighed* after treatment and compared to tissue in mice that had not been treated. Applicants note that histology or counting of metastases was not performed. This data does not show that the treatment caused inhibition of metastasis or reduction in the number of metastases, particularly because compounds such as WR-2721 are well known to delay the growth of normal or cancerous cells as indicated in Kanclerz page 315, right column that reads:

> "This reflects direct toxic activity of the radioprotector on disseminated cells which increases with total dose. WR-2721 has been previously shown to be cytotoxic in vivo [reference omitted]."

The negative control for these toxic effects of the drug on normal tissue was not included in the study. The fact that the authors observed a lower weight for the treated tissue when compared to the untreated tissue is consistent with WR-2721 being a general cell growth inhibitor. Thus, a person of ordinary skill in the art would not consider the Kanclerz reference to have demonstrated an inhibition of metastasis or a reduction in the number of metastases.

Based on the Kanclerz reference, it cannot be determined whether the number of metastases is reduced or whether metastases are inhibited because no investigation of metastasis was undertaken only the effects on established micrometastases. The Kanclerz reference provides an insufficient disclosure, either alone or in combination with Milas, that would permit one of skill in the art to ascertain whether or not the limitations of the present claims are addressed. Therefore, the Milas and Kanclerz references do not provide all elements of the invention, nor do they provide a description of how to make and use the claimed invention in such a manner that one of ordinary skill would be able to practice the claimed invention.

In fact, the Kanclerz reference teaches away from the claimed invention by asserting that reduction of tissue weight is directly proportional to the amount of amifostine drug administered. Applicants note that Figure 4 shows that the dose of 0.05 g/kg is not significantly different from the untreated control organ weights. In two out of the four organ endpoints used, only the 2 g/kg dose, which is beyond the 150 mg/kg recited in the claims, is significantly different from the control values. This closer scrutiny of the data further confirms that the cited reference does not teach the claimed invention when taken alone or in combination with other cited references.

This is in contrast to the present specification. The specification, for example at page 24, lines 1-4, provides data about metastases by measuring both the number of metastases following treatment and evaluates the incidence of metastasis (whether metastasis occurs at all). The specification provides additional information to show that phosphorothioates, in particular aminoalkylphosphorothioates, effect reduction in the number of metastases and inhibit metastasis. Therefore, the Kanclerz reference is not sufficiently enabled, alone or combination with Milas.

Applicants submit that the rejections of claims 1, 3-13, 30, and 31 under 35 U.S.C. § 103(a) are overcome.

**2. Claims 1, 23 and 25-29 are not obvious in light of Milas *et al.*, 1984 in view of Kanclerz *et al.*, 1988; Golub, 1998; and Antras-Ferry *et al.*, 1997.**

For the reasons provided herein the Milas and Kanclerz references do not provide a *prima facie* case of obvious and without these references the combination of Milas, Kanclerz, Golub and Antras-Ferry fails to provide a *prima facie* case of obviousness for claims 1, 23 and 25-29,

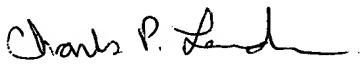
due to the fact that the Golub or the Antras-Ferry references do not remedy the deficiency in the criteria for establishing a prima facie case of obviousness.

### 3. Claims 1, 23 and 24 are not obvious in light of Milas *et al.*, 1984 in view of Kanclerz *et al.*, 1988 and Gately *et al.*, 1997.

For the reasons provided herein the Milas and Kanclerz references do not provide a prima facie case of obvious and without these references the combination of Milas, Kanclerz, and Gately fails to provide a prima facie case of obviousness for claims 1, 23 and 24, due to the fact that the Gately reference does not remedy the deficiency in the criteria for establishing a prima facie case of obviousness..

The Examiner is invited to contact the undersigned patent agent at 512-536-5674 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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**APPENDIX A**
**Claims as Amended**

1. (Three times amended) A method for reducing the number of metastases in an animal exhibiting a primary tumor comprising administering to said animal a [subcytoprotective] dose of 10 mg/kg to 150 mg/kg of an aminoalkylphosphorothioate or active metabolite thereof, wherein the number of metastases is reduced.

8. (Canceled) The method of claim 1, wherein said phosphorothioate is an aminoalkylphosphorothioate compound.

9. (Three times amended) The method claim 1[8], wherein said aminoalkylphosphorothioate is the thiol form.

10. (Three times amended) The method claim 1[8], wherein said aminoalkylphosphorothioate is the disulfide form.

11. (Twice amended) The method of claim 1, wherein said aminoalkylphosphorothioate or active metabolite thereof is selected from the group consisting of WR-2721 (amifostine), WR-1065, WR-638, WR-77913, WR-33278, WR-3689, WR-2822, WR-2529, WR-255591, WR-2823, WR-255709, WR-151326 and WR-151327.

12. (Twice amended) The method of claim 1, wherein the route of administration of said aminoalkylphosphorothioate or active metabolite thereof is intravenous, intraperitoneal, intradermal, intramusculararal, dermal, nasal, buccal, rectal, vaginal, inhalation, or topical.

13. (Twice amended) The method of claim 1, wherein said aminoalkylphosphorothioate or active metabolite thereof is formulated into solutions, suspensions, tablets, pills, capsules, sustained release formulations, powders, creams, ointments, salves, sprays, pumps, liposomes, suppositories, inhalers, and patches.

23. (Amended) The method of claim 1, further comprising monitoring the ability of the [subcytoprotective] dose of an aminoalkylphosphorothioate or active metabolite to reduce metastases in the animal.

30. (Three times amended) A method for inhibiting metastasis in an animal exhibiting a primary tumor comprising administering to said animal a [subcytoprotective] dose of 10 mg/kg to 150 mg/kg of an aminoalkylphosphorothioate or active metabolite thereof, wherein the number of metastases is inhibited.

31. (Three times amended) A method for preventing metastasis in an animal exhibiting a primary tumor comprising administering to said animal a [subcytoprotective] dose of 10 mg/kg to 150 mg/kg of an aminoalkylphosphorothioate or active metabolite thereof, and wherein metastases are prevented in said animal.

32. (Amended) The method of claim 11, wherein said aminoalkylphosphorothioate or active metabolite thereof is WR-2721.

33. (Amended) The method of claim 11, wherein said aminoalkylphosphorothioate or active metabolite thereof is WR-1065.

## APPENDIX B
## Copy Of Claims Currently Pending

1. A method for reducing the number of metastases in an animal exhibiting a primary tumor comprising administering to said animal a dose of 10 mg/kg to 150 mg/kg of an aminoalkylphosphorothioate or active metabolite thereof, wherein the number of metastases is reduced.

3. The method of claim 1, wherein the dose is about 10 mg/kg to about 100 mg/kg.

4. The method of claim 1, wherein the dose is about 10 mg/kg to about 50 mg/kg.

5. The method of claim 1, wherein the dose is about 10 mg/kg to about 25 mg/kg.

6. The method of claim 1, wherein said animal is a human.

7. The method of claim 1, wherein said tumor is a sarcoma or carcinoma.

9. The method claim 1, wherein said aminoalkylphosphorothioate is the thiol form.

10. The method claim 1, wherein said aminoalkylphosphorothioate is the disulfide form.

11. The method of claim 1, wherein said aminoalkylphosphorothioate or active metabolite thereof is selected from the group consisting of WR-2721 (amifostine), WR-1065, WR-638, WR-77913, WR-33278, WR-3689, WR-2822, WR-2529, WR-255591, WR-2823, WR-255709, WR-151326 and WR-151327.

12. The method of claim 1, wherein the route of administration of said aminoalkylphosphorothioate or active metabolite thereof is intravenous, intraperitoneal, intradermal, intramusculararal, dermal, nasal, buccal, rectal, vaginal, inhalation, or topical.

13. The method of claim 1, wherein said aminoalkylphosphorothioate or active metabolite thereof is formulated into solutions, suspensions, tablets, pills, capsules, sustained release formulations, powders, creams, ointments, salves, sprays, pumps, liposomes, suppositories, inhalers, and patches.

23. The method of claim 1, further comprising monitoring the ability of the dose of an aminoalkylphosphorothioate or active metabolite to reduce metastases in the animal.

24. The method of claim 23, wherein the monitoring comprises measuring the level of angiostatin stimulation.

25. The method of claim 23, wherein the monitoring comprises measuring the level of activity of a matrix metalloproteinase.

26. The method of claim 25, wherein the matrix metalloproteinase is MMP-2.

27. The method of claim 25, wherein the matrix metalloproteinase is MMP-9.

28. The method of claim 23, wherein the monitoring comprising measuring the stimulation of MnSOD.

29. The method of claim 28, wherein the measuring of MnSOD stimulation comprises measuring the stimulation of MnSOD gene expression.

30. A method for inhibiting metastasis in an animal exhibiting a primary tumor comprising administering to said animal a dose of 10 mg/kg to 150 mg/kg of an aminoalkylphosphorothioate or active metabolite thereof, wherein the number of metastases is inhibited.

31. A method for preventing metastasis in an animal exhibiting a primary tumor comprising administering to said animal a dose of 10 mg/kg to 150 mg/kg of an aminoalkylphosphorothioate or active metabolite thereof, and wherein metastases are prevented in said animal.

32. The method of claim 11, wherein said aminoalkylphosphorothioate or active metabolite thereof is WR-2721.

33. The method of claim 11, wherein said aminoalkylphosphorothioate or active metabolite thereof is WR-1065.